Remarks

The Amendments

Claims

Claim 1 has been amended to recite separate steps of detecting and comparing in place of a single step of "detecting and comparing."

Claim 1 has also been amended to recite that expression of at least five genes is compared in a "first" relative to a "second" biological sample. The amendment is supported by the specification which discloses preparing biological samples and comparing expression levels of genes between the samples: "A variety of nucleic acid samples are prepared according to the methods of the invention to represent many states of the genetic network. By comparing the expression levels of those samples, regulatory relationships among genes can be determined with a certain statistical confidence." (Page 14, lines 2-3.)

Claim 1 has also been amended in the step of generating to recite that the "cluster map categorizes genes according to similarity in unchanged, increased, or decreased expression in the first relative to the second of said biological samples." This amendment is supported by the specification which discloses categorizing genes whose expression is similarly up- or down-regulated in one sample compared to another: "Expression levels of 137 genes increased in malignant breast cells >10-fold compared to normal breast cells. The expression of a further 167 genes decreased to near undetectable levels. A total of 1,549 expressed genes were detected in the breast cancer cells. A simple categorization of the expression changes revealed patterns." (Page 50, lines 11-15.) This amendment is also

supported by the specification which discloses grouping, *i.e.*, categorizing, genes whose expression is similarly unchanged, up-regulated, or down-regulated in one sample relative to another: "In the middle portion of the Figure a magnified view of a portion of the array highlighting examples of altered gene expression between BT-474 and HT-125 is shown. In area 1, induced (>10-fold change in hybridization intensity) genes are shown, in area 2, unchanged (<2-fold change in hybridization intensity) are shown, and in area 3 repressed (>10-fold change in hybridization intensity) are shown." (Page 6, lines 10-19.)

Claim 2 has been amended to delete the recitation that the expression of genes is detected by measuring the relative amount of transcripts of the genes.

Claim 5 has been amended to recite "cells" in place of "said cells."

Claims 106 and 107 have been amended to properly recite dependency on claim 1 in place of claim 7.

None of these amendments introduce new matter.

Specification

The numbers in parentheses refer to the paragraphs as numbered in the "Amendments to the Specification."

(1) The description of Figure 5 has been amended to add a description of the sequences at the bottom half of the figure. The added sentence, "The genotype analysis shows a G (see 1209_B01.01 and et121701.02 (SEQ ID NO:3)) to A (see et121702.02 (SEQ ID NO:5)) base change resulting in a E (see 1209_B01.01 and et 121701.02 (SEQ ID NO:4)) to K (see et 12702.02 (SEQ ID NO:6))," is supported by the specification which

discloses: "Figure 5 shows the results of the genotypic analysis demonstrating that there was a G to A base change resulting in a E to K amino acid change at position 285 in exon 8, the p53 DNA binding domain." (Page 43, lines 19-21.) The sentence also includes references to the sequences that appear in the figure and their corresponding SEQ ID NOs: in the sequence listing.

(2) The specification has also been amended to delete the description of Figure 8, at page 6, lines 1-2, which does not match Figure 8.

(3), (4), and (5) The specification has been amended at page 6, lines 3-21 to describe Figure 8 in place of Figure 9. The specification has been amended at page 6, lines 22-26 to describe Figure 9A and B in place of Figure 10. The specification has been amended at page 6, line 27 to page 7, line 11 to describe Figure 10A, B, and C in place of Figure 11. These amendments merely match the Figure descriptions with their corresponding Figures.

(5) The description of Figure 10 has further been amended to refer to the SEQ ID NOs: in the sequence listing that correspond to each of the sequences that appear in the figure.

(6) The specification has been amended to add a sentence that describes Figure 11A-M. The description is a reference to the title of the Table that appears in Figure 11A-M.

(7) The specification has been amended to correct a typographical error, "purposed" has been replaced with "purposes."

(8) and (9) The specification has been amended to remove all embedded hyperlinks. Each hyperlink has been replaced with a written description of the Uniform Resource Locator, or web address, that accesses each hyperlink. For instance, "http://www.ncbi.nlm.nih.gov" has been amended to "URL address: http file type, www host server, ncbi.nlm.nih.gov domain name."

(10), (11), and (12) The specification has been amended at paragraphs that describe p53 DNA array analysis and sequencing in BT-474 and HT-125 cells. The description has been amended to refer to Figure 10A, B, and C in place of Figure 3A and B. Figure 10A, B, and C also shows DNA array analysis and sequencing of p53 in BT-474 and HT-125 cells. Figure 3 does not.

(13) and (15) The specification has been amended to add a sequence identifier immediately following each disclosed sequence in the description.

(14) The specification has been amended to delete a reference to Table 4, which is not disclosed in the application.

(15) A sequence listing has been added immediately following the claims. The sequences disclosed in the sequence listing are identical to the sequences disclosed in paragraphs (13) and (15), and Figures 5 and 10C of the application.

None of the amendments introduce new matter.

Objections to the Drawings

A set of revised, formal, drawings accompany this amendment to correct any deficiencies in the drawings.

Withdrawal of this objection is respectfully requested.

Objections to the Disclosure

The disclosure has been objected to for containing informalities. Each informality is discussed in the order in which it appears in the Office Action.

The disclosure has been objected to because the description of Figures 10 and 11 does not refer to all the subparts shown in Figures 10 and 11. (Paper 11, page 6, lines 3-4.) The specification has been amended to correctly describe Figure 10 and to refer to each of subparts, A-C. The specification has further been amended to add a description of Figure 11 that refers each of its subparts, A-M

The disclosure has also been objected to because the application does not contain Figures 3A and 3B, but the specification refers to Figure 3A on page 58 at line 28 and Figure 3B on page 59 at lines 1, 3, and 4. (Paper 11, page 6, lines 5-8.) The specification has been amended to correctly refer to Figure 10A, B, or C at these citations in place of Figure 3A or 3B.

The disclosure has also been objected to for referring to Table 4 because the application does not disclose a Table 4. (Paper 11, page 6, lines 9-10.) The reference to Table 4 has been deleted.

The disclosure has also been objected to for containing embedded hyperlinks and/or other forms of browser executable code. (Paper 11, page 6, lines 11-12.) The embedded hyperlinks have been deleted from the specification and replaced with descriptions of their website location in the uniform resource locator.

Withdrawal of these objections to the disclosure is respectfully requested.

Sequence Compliance

The application has been objected to as disclosing sequences in the specification that are encompassed by the definitions for nucleotide and/or amino acid sequences as set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2), but as not containing a sequence listing. Applicants submit a sequence listing in paper and computer readable format to comply with 37 C.F.R. § 1.821 through 37 C.F.R. § 1.825.

The sequence listing introduces no new matter. The content of the paper and computer readable format of the sequence listing is the same.

The specification has also been amended at each sequence disclosure to contain a reference to its assigned sequence identifier in the sequence listing.

Withdrawal of this objection is respectfully requested.

The Rejection of Claims 1-9, 106, and 107 Under 35 U.S.C. § 112, First Paragraph

Claims 1-9, 106, and 107 are rejected under 35 U.S.C. § 112, first paragraph, as not enabled by the specification. Applicants respectfully traverse.

Claim 1 is the only independent claim of the rejected claim set. Claim 1 recites a method for mapping a gene network. A plurality of biological samples is prepared. Expression of a least five genes is detected in the biological samples. Expression of the at least five genes in a first of said biological samples is compared to expression of the at least five genes in a second of said biological samples. A cluster map is generated for the

genes. The cluster map categorizes genes according to similarity in unchanged, increased, or decreased expression in the first relative to the second of the biological samples. The cluster map is analyzed to generate gene network causal models defining regulator relationships among the genes.

To satisfy the enablement requirement, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). A specification need not disclose what is well known to those skilled in the art and preferably omits that which is well known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

The Office Action asserts that the specification does not enable the claims because it does not disclose specific procedures or steps that teach: "particularly how and to what is gene expression compared; 2) how the cluster map is generated; 3) what is and how to determine correlation of expression; and 4) how gene network causal models are generated." (Paper 11, page 4, lines 18-20.) The Office Action also asserts that the step of analyzing is not enabled because the specification does not provide any procedural steps for the analysis of the cluster map. (Paper 11, page 5, lines 1-3.) Each of these allegations will be discussed in turn.

1) How and to what gene expression is compared.

Methods for comparing gene expression were well known in the art at the time the application was filed. Gene expression, according to the amended claim, is compared by

determining expression of a plurality of genes in each of a plurality of samples and comparing expression of the genes in a first sample to expression of the genes in a second sample. Methods of determining expression of a gene in a sample were well known in the art at the time the application was filed. The specification discloses numerous methods of determining gene expression in a sample. The specification discloses:

> In addition to high density nucleic acid arrays, other methods are also useful for massive gene expression monitoring. Differential display, described by Liang, P. and Pardee, A.B. (Differential Display of eukaryotic messenger RNA by means of the polymerase chain reaction. *Science* 257:967-971, 1992, incorporated herein by reference for all purposes) provides a useful mean for distinguishing gene expression between two samples. Serial analysis of gene expression, described by Velculescu et al. (Serial Analysis of Gene Expression. Science, 270:484-487, 1995, incorporated herein by reference for all purposes) provides another method for quantative and qualitative analysis of gene expression. Optical fiber oligonucleotide sensors, described by Ferguson et al. (A Fiber-optic DNA biosensor microarray for the analysis of gene expression. Nature-Biotechnology 14:1681-1684, 1996), can also be used for gene expression monitoring.

Page 37, line 27 to page 38, line 3. The specification also discloses that gene expression can be determined by detecting "protein products using procedures such as Western blotting and immunocytochemistry. Other immunological methods can also be used." (Page 20, lines 13-14.)

Methods for comparing expression of the gene in the first sample to expression of the gene in the second sample were well known at the time of filing. These methods included determining the absolute amount of a gene product expressed by each of the samples, *e.g.*, ng or μg quantities of transcript or polypeptide, and using simple

mathematics (division) to determine the amount of increase or decrease in expression in the first relative to the second sample. The simple mathematical calculations can be performed using a machine such as a calculator or computer, or by hand. It would not have required undue experimentation for one of skill in the art to determine gene expression of at least five genes in biological samples and to determine a difference in expression of each of the at least five genes in the first relative to the second sample in the plurality of biological samples.

Claim 1 has been amended to recite "comparing expression of the at least five genes in a first of said biological samples to expression of the at least five genes in a second of said biological samples." Thus the amended claims specify that gene expression is compared for a gene in a first sample to expression of the gene in a second sample. No experimentation would have been required for one of skill in the art to determine to what gene expression is compared in claims 1-9, 106, and 107.

2) How the cluster map is generated.

Amended claim 1 recites how a cluster map is generated. Claim 1 recites that a "cluster map categorizes genes according to similarity in unchanged, increased, or decreased expression in the first relative to the second of said biological samples." Thus genes are clustered if their expression is altered in a similar manner in the first relative to the second sample or is unaltered in the first relative to the second sample. One of skill in the art could readily have generated a cluster map by identifying and clustering genes whose expression is unchanged in the first biological sample relative to the second biological sample. Alternatively, one of skill in the art would have been able to cluster

genes whose expression is up- or down-regulated in the first sample relative to the second sample. Alternatively, one of skill in the art would have been able to cluster genes whose expression is up- or down-regulated by a similar fold difference in the first relative to a second sample. The specification discloses, "Comparison of hybridization signal intensities, that ranged over 4-orders of magnitude, revealed all categories of message expression changes including repressed (>10-fold down), down-regulated (<10-fold down), up-regulated (<10-fold up) and induced (>10-fold up) mRNAs between normal and malignant cells." (Page 52, line 33 to page 53, line 4.) In addition, one of skill in the art would also have been able to employ more than one of these clustering strategies to generate a cluster map. It would not have required undue experimentation for one of skill in the art to cluster genes as recited in the rejected claims.

3) What is and how to determine correlation of expression.

The recitation "correlation in expression" has been deleted. Thus this issue is moot.

4) How gene network causal models are generated.

Claim 1 recites how gene network causal models are generated: "analyzing said cluster map to generate gene network causal models." The Office Action asserts that analyzing a cluster map is not enabled because the specification does not provide any procedural steps for performing this step. (Paper 11, page 5, lines 1-3.)

The specification need not provide procedural steps for analyzing a cluster map because such methods were well known in the art and were publicly available at the time the application was filed. The specification discloses,

> Methods for cluster analysis are described in detail in Hartigan (1975) Clustering Algorithms, NY, John Wile and Sons, Inc, and Everritt, (1980) Cluster Analysis 2nd. Ed. London Heineman Educational books, Ltd., incorporated herein for all purposes by reference. The causal relationships in a genetic network can also be modeled by stochastic procedures. Such models allow the examination of the dynamical aspects of the genetic network in terms of change over time or across conditions. Maybeck, Stochastic Models, estimation and control, vol. 1, (1979) NY, Academic Press.

Page 40, lines 6-13. The specification also discloses using the well known LISREL model to analyze a cluster map:

> LISREL is a very general approach for causal model analysis. It allows latent or hidden (not measurable) variables. Therefore, in some embodiments, latent variables are used to account for unmeasured genes or regulatory relations. LISREL models also allow bidirectional or reciprocal causation, measurement errors and correlated residuals. Mathematical theories and applications of LISREL are described in detail in Joreskog and Sorbom (1979) Advances in Factor Analysis and Structural Equations Modeling, Cambridge MA, Abt Books; and Joreskog and Sorbom, (1985) LISREL, VI: Analysis of Linear Structural Relationships by Maximum Likelihood Instrumental Variables and Least Squares, Uppsala, Sweden: University of Uppsala, incorporated herein by reference for all purposes. Computer implementations of LISREL are provided by numerous other software packages.

Page 40, lines 23-33. Thus the specification discloses well known methods for cluster map analysis which date back to the 1970's and 1980's. These methods were publicly available. One of skill in the art, having knowledge of these methods, would have readily been able to perform analysis of a cluster map to generate gene network causal models without undue experimentation.

Withdrawal of the enablement rejection to claims 1-9, 106, and 107 is respectfully requested.

The Rejection of Claims 2 and 5 Under 35 U.S.C. § 112, Second Paragraph

Claims 2 and 5 have been rejected under 35 U.S.C. § 112, second paragraph, as not being definite.

The Office Action asserts that claim 2 is indefinite for reciting "measuring the relative and/or absolute amount of transcript of said genes." The Office Action asserts that "relative" is indefinite because it is not clear to what the measured amount of gene transcript is relative, nor is it clear what the limitations of "relative" are. (Paper 11, page 5, lines 16-18.) Claim 2 has been amended to delete the recitation of "relative." Thus the rejection is rendered moot.

The Office Action asserts that the recitation "said cells" is unclear in claim 5 because "cells" lacks antecedent basis in claim 1, the claim from which it depends. Claim 5 has been amended to recite "cells" in place of "said cells."

Withdrawal of these rejections to claims 2 and 5 is respectfully requested.

Respectfully submitted,

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